CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074835

Trade Name : NORTRIPTYLINE HYDROCHLORIDE CAPSULE USP

Generic Name: Nortriptyline Hydrochloride Capsule USP 10mg (base), 25mg (base), 50mg (base) and 75mg (base)

Sponsor : Invamed, Inc.

Approval Date: June 30, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074835

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074835

APPROVAL LETTER

ANDA 74-835

JUN 30 1997

Invamed Inc.
Attention: Mahendra B. Patel, Ph.D.
2400 Rt. 130 North
Dayton, NJ 08810

Dear Dr. Patel:

This is in reference to your abbreviated new drug application dated January 13, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Nortriptyline Hydrochloride Capsules USP, 10 mg (base), 25 mg (base), 50 mg (base) and 75 mg (base).

Reference is also made to your amendments dated August 17, 1996; April 29, 1997 and May 21, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Nortriptyline Hydrochloride Capsules USP, 10 mg (base), 25 mg (base), 50 mg (base), and 75 mg (base) to be bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Pamelor® Capsules, 10 mg (base), 25 mg (base), 50 mg (base), and 75 mg (base), respectively, of Novartis Pharmaceutical Corporation). Your dissolution testing should be incorporated into the stability and quality control programs using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 6/30/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074835

FINAL PRINTED LABELING

NDC 52189-330-29

invamed inc.

Nortriptyline Hydrochloride Capsules, USP

50 mg*

CAUTION: Federal law prohibits dispensing without prescription.

500 CAPSULES

***EACH CAPSULE CONTAINS:**
Nortriptyline Hydrochloride equivalent to 50 mg Nortriptyline.

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight container as defined in the USP, with a child-resistant closure.

Store below 30°C (86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-330-29 5

Lot No.:
Exp. Date:
MF # 868

NDC 52189-330-30

invamed inc.

Nortriptyline Hydrochloride Capsules, USP

50 mg*

CAUTION: Federal law prohibits dispensing without prescription.

1000 CAPSULES

***EACH CAPSULE CONTAINS:**
Nortriptyline Hydrochloride equivalent to 50 mg Nortriptyline.

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight container as defined in the USP, with a child-resistant closure.

Store below 30°C (86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-330-30 1

Lot No.:
Exp. Date:
MF # 869

NDC 52189-330-24

invamed inc.

Nortriptyline Hydrochloride Capsules, USP

50 mg*

CAUTION: Federal law prohibits dispensing without prescription.

100 CAPSULES

***EACH CAPSULE CONTAINS:**
Nortriptyline Hydrochloride equivalent to 50 mg Nortriptyline.

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight container as defined in the USP, with a child-resistant closure.

Store below 30°C (86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-330-24 0

Lot No.:
Exp. Date:
MF # 867

NDC 52189-331-24

invamed inc.

Nortriptyline Hydrochloride Capsules, USP

75 mg*

CAUTION: Federal law prohibits dispensing without prescription.

100 CAPSULES

***EACH CAPSULE CONTAINS:**
Nortriptyline Hydrochloride equivalent to 75 mg Nortriptyline.

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight container as defined in the USP, with a child-resistant closure.

Store below 30°C (86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-331-24 7

Lot No.:
Exp. Date:
MF # 870

NDC 52189-331-30

invamed inc.

Nortriptyline Hydrochloride Capsules, USP

75 mg*

CAUTION: Federal law prohibits dispensing without prescription.

1000 CAPSULES

***EACH CAPSULE CONTAINS:**
Nortriptyline Hydrochloride equivalent to 75 mg Nortriptyline.

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight container as defined in the USP, with a child-resistant closure.

Store below 30°C (86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-331-30 8

Lot No.:
Exp. Date:
MF # 872

NDC 52189-331-29

invamed inc.

Nortriptyline Hydrochloride Capsules, USP

75 mg*

CAUTION: Federal law prohibits dispensing without prescription.

500 CAPSULES

***EACH CAPSULE CONTAINS:**
Nortriptyline Hydrochloride equivalent to 75 mg Nortriptyline.

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight container as defined in the USP, with a child-resistant closure.

Store below 30°C (86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-331-29 2

Lot No.:
Exp. Date:
MF # 871

NDC 52189-328-30

invamed inc.

Nortriptyline Hydrochloride Capsules, USP

10 mg*

CAUTION: Federal law prohibits dispensing without prescription.

1000 CAPSULES

***EACH CAPSULE CONTAINS:**
Nortriptyline Hydrochloride equivalent to 10 mg Nortriptyline.

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight container as defined in the USP, with a child-resistant closure.

Store below 30°C (86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-328-30 8

Lot No.:
Exp. Date:
MF # 863

NDC 52189-328-29

invamed inc.

Nortriptyline Hydrochloride Capsules, USP

10 mg*

CAUTION: Federal law prohibits dispensing without prescription.

500 CAPSULES

***EACH CAPSULE CONTAINS:**
Nortriptyline Hydrochloride equivalent to 10 mg Nortriptyline.

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight container as defined in the USP, with a child-resistant closure.

Store below 30°C (86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-328-29 2

Lot No.:
Exp. Date:
MF # 862

NDC 52189-328-24

invamed inc.

Nortriptyline Hydrochloride Capsules, USP

10 mg*

CAUTION: Federal law prohibits dispensing without prescription.

100 CAPSULES

***EACH CAPSULE CONTAINS:**
Nortriptyline Hydrochloride equivalent to 10 mg Nortriptyline.

USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight container as defined in the USP, with a child-resistant closure.

Store below 30°C (86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

N 3 52189-328-24 7

Lot No.:
Exp. Date:
MF # 861

NDC 52189-329-24

invamed inc.

Nortriptyline Hydrochloride Capsules, USP

25 mg*

CAUTION: Federal law prohibits dispensing without prescription.

100 CAPSULES

***EACH CAPSULE CONTAINS:**
Nortriptyline Hydrochloride equivalent to 25 mg Nortriptyline.

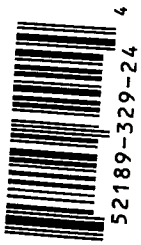
USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight container as defined in the USP, with a child-resistant closure.

Store below 30°C (86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



Lot No.:
Exp. Date:
MF # 864

NDC 52189-329-30

invamed inc.

Nortriptyline Hydrochloride Capsules, USP

25 mg*

CAUTION: Federal law prohibits dispensing without prescription.

1000 CAPSULES

***EACH CAPSULE CONTAINS:**
Nortriptyline Hydrochloride equivalent to 25 mg Nortriptyline.

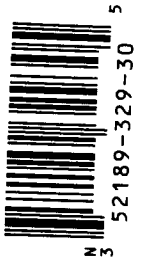
USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight container as defined in the USP, with a child-resistant closure.

Store below 30°C (86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA



Lot No.:
Exp. Date:
MF # 866

NDC 52189-329-29

invamed inc.

Nortriptyline Hydrochloride Capsules, USP

25 mg*

CAUTION: Federal law prohibits dispensing without prescription.

500 CAPSULES

***EACH CAPSULE CONTAINS:**
Nortriptyline Hydrochloride equivalent to 25 mg Nortriptyline.

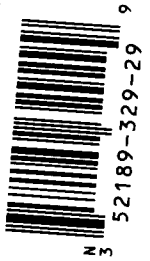
USUAL DOSAGE: See accompanying prescribing information.

Keep this and all drugs out of the reach of children.

Dispense in a tight container as defined in the USP, with a child-resistant closure.

Store below 30°C (86°F).

Manufactured By:
INVAMED INC., Dayton, NJ 08810 USA

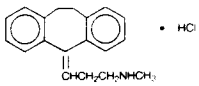


Lot No.:
Exp. Date:
MF # 865

NORTRIPTYLINE HYDROCHLORIDE CAPSULES, USP

DESCRIPTION

Nortriptyline hydrochloride is 10,11-Dihydro-*N*-methyl-5*H*-dibenzo[*a,d*]cycloheptene-Δ^5,γ-propylamine hydrochloride. The structural formula is as follows:



$C_{19}H_{21}N \cdot HCl$ M.W. 299.85

Nortriptyline hydrochloride is a white to off-white powder, having a slight characteristic odor. It is soluble in water and chloroform; sparingly soluble in methanol; and practically insoluble in most organic solvents.

Each capsule, for oral administration, contains nortriptyline hydrochloride equivalent to 10 mg, 25 mg, 50 mg or 75 mg of nortriptyline.

In addition each capsule contains the *following inactive ingredients*: gelatin, magnesium stearate, pregelatinized starch, silicon dioxide, sodium lauryl sulfate and titanium dioxide. The 10 mg, 25 mg and 75 mg capsules also contain FD&C Blue No.1 and D&C Yellow No.10. The 10 mg, 25 mg and 50 mg capsules also contain synthetic black iron oxide dye in the imprinting ink.

CLINICAL PHARMACOLOGY

The mechanism of mood elevation by tricyclic antidepressants is at present unknown. Nortriptyline hydrochloride is not a monoamine oxidase inhibitor. It inhibits the activity of such diverse agents as histamine, 5-hydroxytryptamine, and acetylcholine. It increases the pressor effect of norepinephrine but blocks the pressor response of phenethylamine. Studies suggest that nortriptyline interferes with the transport, release, and storage of catecholamines. Operant conditioning techniques in rats and pigeons suggest that nortriptyline has a combination of stimulant and depressant properties.

INDICATIONS AND USAGE

Nortriptyline hydrochloride capsules are indicated for the relief of symptoms of depression. Endogenous depressions are more likely to be alleviated than are other depressive states.

CONTRAINDICATIONS

The use of nortriptyline hydrochloride or other tricyclic antidepressants concurrently with a monoamine oxidase (MAO) inhibitor is contraindicated. Hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations. It is advisable to have discontinued the MAO inhibitor for at least two weeks before treatment with nortriptyline is started. Patients hypersensitive to nortriptyline should not be given the drug.

Cross-sensitivity between nortriptyline and other dibenzazepines is a possibility.

Nortriptyline is contraindicated during the acute recovery period after myocardial infarction.

WARNINGS

Patients with cardiovascular disease should be given nortriptyline hydrochloride only under close supervision

line and other benzodiazepines is a possibility.

Nortriptyline is contraindicated during the acute recovery period after myocardial infarction.

WARNINGS

Patients with cardiovascular disease should be given nortriptyline hydrochloride only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong the conduction time. Myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely when nortriptyline is administered, in as much as this drug is known to lower the convulsive threshold. Great care is required if nortriptyline is given to hyperthyroid patients or to those receiving thyroid medication, since cardiac arrhythmias may develop.

Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly.

Excessive consumption of alcohol in combination with nortriptyline therapy may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher AUC and lower clearance of nortriptyline.

Use in Pregnancy

Safe use of nortriptyline hydrochloride during pregnancy and lactation has not been established; therefore, when the drug is administered to pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards. Animal reproduction studies have yielded inconclusive results.

Use in Children

This drug is not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

PRECAUTIONS

General

The use of nortriptyline hydrochloride in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms. If the drug is given to overactive or agitated patients, increased anxiety and agitation may occur. In manic-depressive patients, nortriptyline may cause symptoms of the manic phase to emerge.

Troublesome patient hostility may be aroused by the use of nortriptyline. Epileptiform seizures may accompany its administration, as is true of other drugs of its class.

When it is essential, the drug may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery.

The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time.

Both elevation and lowering of blood sugar levels have been reported.

Drug Interactions

Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients.

Close supervision and careful adjustment of the dosage are required when nortriptyline is used with other anticholinergic drugs and sympathomimetic drugs.

Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. The patient should be informed that the response to alcohol may be exaggerated.

A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

Drugs Metabolized by P450 2D6

The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7 to 10% of caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make

that the least possible quantity of drug be dispensed at any given time.

Both elevation and lowering of blood sugar levels have been reported.

Drug Interactions

Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients.

Close supervision and careful adjustment of the dosage are required when nortriptyline is used with other anticholinergic drugs and sympathomimetic drugs.

Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. The patient should be informed that the response to alcohol may be exaggerated.

A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

Drugs Metabolized by P450 2D6

The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7 to 10% of caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be co-administered with another drug known to be an inhibitor of P450 2D6.

ADVERSE REACTIONS

Note: Included in the following list are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when nortriptyline is administered.

Cardiovascular - Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric - Confusional states (especially in the elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis.

Neurologic - Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus.

Anticholinergic - Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.

Allergic - Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever; cross-sensitivity with other tricyclic drugs.

Hematologic - Bone marrow depression, including agranulocytosis; eosinophilia; purpura; thrombocytopenia.

Gastrointestinal - Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black tongue.

Endocrine - Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other - Jaundice (simulating obstructive); altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia.

Withdrawal Symptoms - Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

OVERDOSAGE

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As the management is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose, therefore, hospital monitoring is required as soon as possible.

Manifestations:

Critical manifestations of overdose include: cardiac dysrhythmias, severe hypotension, shock, congestive heart failure, pulmonary edema, convulsions, and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity.

Other signs of overdose may include: confusion, restlessness, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or any of the acute symptoms listed under **ADVERSE REACTIONS**. There have been reports of patients recovering from nortriptyline overdoses of up to 525 mg.

Management:

General

Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of six hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination

All patients suspected of tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular

A maximal limb-lead QRS duration of ≥0.10 seconds may be the best indication of the severity of the overdose. Serum alkalinization, to a pH of 7.45 to 7.55, using intravenous sodium bicarbonate and hyperventilation, (as needed) should be instituted for patients with dysrhythmias and/or QRS widening. A pH >7.60 or a pCO_2 <20mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients

A maximal limb-lead QRS duration of ≥0.10 seconds may be the best indication of the severity of the overdose. Serum alkalinization, to a pH of 7.45 to 7.55, using intravenous sodium bicarbonate and hyperventilation, (as needed) should be instituted for patients with dysrhythmias and/or QRS widening. A pH >7.60 or a pCO_2 <20mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported ineffective in tricyclic antidepressant poisoning.

CNS

In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants, (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control center.

Psychiatric Follow-up

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

Pediatric Management

The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

DOSAGE AND ADMINISTRATION

Nortriptyline hydrochloride is not recommended for children.

Lower than usual dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients than for hospitalized patients who will be under close supervision. The physician should initiate dosage at a low level and increase it gradually, noting carefully the clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a longer period of time at the lowest dose that will maintain remission.

If a patient develops minor side effects, the dosage should be reduced. The drug should be discontinued promptly if adverse effects of a serious nature or allergic manifestations occur.

Usual adult dose

25 mg three or four times daily; dosage should begin at a low level and be increased as required. As an alternate regimen, the total daily dosage may be given once a day. When doses above 100 mg daily are administered, plasma levels of nortriptyline should be monitored and maintained in the optimum range of 50-150 ng/mL. Doses above 150 mg per day are not recommended.

Elderly and Adolescent Patients

30 to 50 mg per day, in divided doses, or the total daily dosage may be given once a day.

HOW SUPPLIED

Nortriptyline Hydrochloride Capsules, USP (equivalent to 10 mg Nortriptyline) are opaque deep green/opaque white capsules, imprinted NORTRIPTYLINE and INV over 10 mg in black are supplied as follows:

NDC 52189-328-24 in bottles of 100 capsules

NDC 52189-328-29 in bottles of 500 capsules

NDC 52189-328-30 in bottles of 1000 capsules

Nortriptyline Hydrochloride Capsules, USP (equivalent to 25 mg Nortriptyline) are opaque deep green/opaque white capsules, imprinted NORTRIPTYLINE and INV over 25 mg in black are supplied as follows.

NDC 52189-329-24 in bottles of 100 capsules

NDC 52189-329-29 in bottles of 500 capsules

NDC 52189-329-30 in bottles of 1000 capsules

Nortriptyline Hydrochloride Capsules, USP (equivalent to 50 mg Nortriptyline) are opaque white/opaque white capsules, imprinted NORTRIPTYLINE and INV over 50 mg in black are supplied as follows:

NDC 52189-330-24 in bottles of 100 capsules

NDC 52189-330-29 in bottles of 500 capsules

NDC 52189-330-30 in bottles of 1000 capsules

Nortriptyline Hydrochloride Capsules, USP (equivalent to 75 mg Nortriptyline) are opaque deep green/opaque deep green capsules, imprinted NORTRIPTYLINE and INV over 75 mg in white are supplied as follows:

NDC 52189-331-24 in bottles of 100 capsules

NDC 52189-331-29 in bottles of 500 capsules

NDC 52189-331-30 in bottles of 1000

HOW SUPPLIED

Nortriptyline Hydrochloride Capsules, USP (equivalent to 10 mg Nortriptyline) are opaque deep green/opaque white capsules, imprinted NORTRIPTYLINE and INV over 10 mg in black are supplied as follows:

NDC 52189-328-24 in bottles of 100 capsules
NDC 52189-328-29 in bottles of 500 capsules
NDC 52189-328-30 in bottles of 1000 capsules

Nortriptyline Hydrochloride Capsules, USP (equivalent to 25 mg Nortriptyline) are opaque deep green/opaque white capsules, imprinted NORTRIPTYLINE and INV over 25 mg in black are supplied as follows:

NDC 52189-329-24 in bottles of 100 capsules
NDC 52189-329-29 in bottles of 500 capsules
NDC 52189-329-30 in bottles of 1000 capsules

Nortriptyline Hydrochloride Capsules, USP (equivalent to 50 mg Nortriptyline) are opaque white/opaque white capsules, imprinted NORTRIPTYLINE and INV over 50 mg in black are supplied as follows:

NDC 52189-330-24 in bottles of 100 capsules
NDC 52189-330-29 in bottles of 500 capsules
NDC 52189-330-30 in bottles of 1000 capsules

Nortriptyline Hydrochloride Capsules, USP (equivalent to 75 mg Nortriptyline) are opaque deep green/opaque deep green capsules, imprinted NORTRIPTYLINE and INV over 75 mg in white are supplied as follows:

NDC 52189-331-24 in bottles of 100 capsules
NDC 52189-331-29 in bottles of 500 capsules
NDC 52189-331-30 in bottles of 1000 capsules

Dispense in a tight container, as defined in the USP with a child-resistant closure.

Store below 30°C (86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by:
INVAMED, INC.
Dayton, NJ 08810 USA

Date of Revision: April 1997
[L-976; MF#873C]

0 976331 9

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074835

CHEMISTRY REVIEW(S)

Office of Generic Drugs

Division of Chemistry II

1. CHEMIST'S REVIEW NO. 3

2. ANDA #74-835

3. NAME AND ADDRESS OF APPLICANT
Invamed Inc.,
Attention: Mahendra B. Patel, Ph.D.
2400 Rt. 130 North
Dayton, NJ 08810

4. LEGAL BASIS for ANDA SUBMISSION
Innovator Products: Aventyl HCl and Pamelor/Sandoz Pharmaceutical Co.; Patent Expires November, 1992; No exclusivity remaining. - page 7

5. SUPPLEMENT(s) None

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Nortriptyline HCl Capsules, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

01.13.96 - Original Submission
02.07.96 - Amendment
08.17.96 - Amendment
09.25.96 - Amendment (labeling)
02.11.97 - New correspondence (CGMP satisfactory)
04.29.97 - Amendment **Subject of this review.**
05.21.97 - Telephone amendment **Subject of this review**

FDA:

06.20.96 - NA letter #1
04.14.97 - NA letter #2 (Facsimile)

10. PHARMACOLOGICAL CATEGORY
Antidepressant

11. Rx or OTC
R_x

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

13. DOSAGE FORM
Capsule

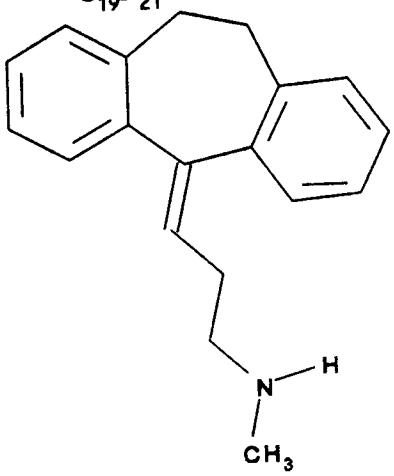
14. POTENCIES
10, 25, 50 and 75 mg

ANDA 74-835/Invamed

15. CHEMICAL NAME AND STRUCTURE

Nortriptyline Hydrochloride USP

$C_{19}H_{21}N.HCl$; M.W. = 299.84



• HCl

10,11-Dihydro-N-methyl-5H-dibenzo[a,d]cycloheptene-Δ^{5},γ-propylamine hydrochloride. CAS [894-71-3]

16. RECORDS AND REPORTS None

17. COMMENTS

a. Manufacturing and Processing is satisfactory in [redacted]

(b)(4) - Confidential Business

b. MV not required; compendial [redacted] tests and specifications are compendial, methods are in-house but provides results comparable to compendial method.

c. Establishment evaluation requested 6.18.96; satisfactory per DO letter dated 02.06.97.

d. Bio-review acceptable, A. Jackson, 6.10.96.

e. Labeling review satisfactory, C. Holquist, 5.13.97

18. CONCLUSIONS AND RECOMMENDATIONS

The application has ~~chemistry~~ no and labeling deficiencies and is ~~NOT~~ APPROVABLE ~~(minor)~~.

19. REVIEWER: U. V. Venkataram

DATE COMPLETED: 05.28.97